HEREDITY AND MUTATION AS CELL PHENOMENA*

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Heredity is frequently defined as the tendency of like to beget like; and the degree of resemblance between parent and offspring is often considered to be a measure of inheritance. The modern Mendelian work with dominant and recessive characters has, however, rendered such definitions incomplete and therefore untenable, since a plant or an animal may inherit in a predictable manner characters which its immediate ancestors did not exhibit at all. Two white races of sweet pea may on crossing give rise to a purple race, a reversion to an ancestral type which in the absence of definite knowledge might have been looked upon as an unexpected variation. But breeding experiments with the two white races will show that their germinal constitution is different. The interpretation then follows that the purple character is not a variation but is a result of inheritance. What has been inherited, however, is not a similarity but a difference.

In similar fashion the French zoologist Cuénot found that in certain cases where a wild gray mouse is crossed with an albino the second generation of offspring contain not only the two original types but black as well, the frequency being 9 gray: 3 black: 4 albino. Breeding experiments with the albino parent disclosed the fact that some of the germ cells of the albino carried the potentiality of producing black under certain conditions, *i. e.*, when meeting a germ cell containing the capacity or factor for developing color. Again we are dealing with phenomena of inheritance not of similarities but of differences. In the same way, in all sexually reproduced organisms it is not the similarities but the differences between the ancestors, or between the offspring, that we remark upon as being inherited. We can only speak of a boy inheriting his father's shape of nose or his mother's color of eyes when his parents differ in these attributes.

It has therefore become necessary to reverse in a sense the usual point of view with regard to heredity. Since it is inaccurate to say that heredity is measured by the degree of resemblance between

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parent and offspring, we may state that heredity consists in the perpetuation of the *differences* between related organisms. Inheritance is then the process by which these differences are perpetuated from generation to generation. This manner of statement is particularly useful when we contrast heredity and variation from the evolutionary point of view. For we may then define variation as the process by which new differences arise, and inheritance as the process by which they are perpetuated.

These definitions have much more biological usefulness than may at first appear. They enable us to compare the phenomena of heredity and variation from a different point of view.

Though the above definition of variation applies to all kinds of variations, yet it has in view particularly mutations, which are completely inherited. We may classify variations as regards their heritability, into three classes: (1) those which are completely inherited, (2) those which are non-inherited, (3) those which are partially inherited. These three classes of variations must then have very different evolutionary significance. It is obvious that completely inherited variations, or mutations, are immediately effective for evolution or at least for species-formation, though it does not necessarily follow that they are of greatest evolutionary significance. It is not necessary to enter into this question here, nor discuss the relative importance of classes (1) and (3),—matters which are still to a large extent in dispute. We may, however, point out that bathmic variations, such as the rectigradations of Osborn, may come in a different category still as regards their relation to evolutionary processes.

The relative evolutionary significance of mutations and continuous or partially-inherited variations can be determined in part by comparison of specific differences in particular groups with the mutations which occur in those groups. Although a mere beginning has as yet been made in this direction, yet it would appear that mutations have probably played a larger part in specific differentiation in some groups than in others. But it will be a long time before these questions can be definitely decided. We may, however, affirm without doubt that in many groups mutations have played an important and even a preponderant part in species formation. Therefore whatever place may ultimately be assigned to mutation in the hierarchy of evolutionary factors in relation to the paleontological history of organisms, it has undoubtedly played an important rôle in the process of speciation.

Considering now certain features of mutations as we know them, one of the most interesting is their variety. Many attempts have been made to explain all mutations in terms of one idea. These universal explanations have involved (1) redistribution of Mendelian characters, (2) loss of factors, (3) reduplication of gametes, and many other hypotheses. They have nearly all, however, involved the idea of the mere loss of qualities or the recombination of those already existing. Such views have been brilliantly advocated, particularly by Mendelian writers. But they consider the phenomena of mutation largely from the outside. The cytological and anatomical combined with the experimental investigation of particular mutations already reveals that mutations belong in various categories and are the result of different types of change.[1]

Germinal changes are not due merely to plus or minus variations, in the loss or addition of Mendelian factors; but on the other hand each change results from a morphological or physiological alteration affecting one element of the germ plasm. This being the case, there is plenty of material at hand for progressive and divergent evolution, and it is unnecessary to imagine that the endless variety of organic structure has resulted from successive germinal simplifications by means of loss.

In a brief analysis of the various known types of germinal change, they may be classified into (1) those which are fundamentally morphological and (2) those which are primarily chemical. It may be expected in general that these two classes of changes will frequently be inherited in different ways. This brings us to the question of the relation between heredity and particular variations in another aspect. We have already observed that variation has to do with the *origin* of differences between organisms, and heredity with the *perpetuation* of those differences. It may here be pointed out that in the inheritance of any character-difference such as we are considering, there are two features to be taken into account; (1) the nature of the character itself, and (2) the mechanism of its inheritance. It is true that in Mendelian inheritance the mechanism by which the germinal determiners of the various character-differences are distributed in the germ cells during meiosis is the chief feature to be considered. But since it is now clear that in certain cases these characters are diluted and

[1] For a discussion of this subject see Gates, The Mutation Factor in Evolution, Chap. IX. MacMillans: London. 1915.

otherwise modified by crossing, the nature of the character and the possibility of its modification through hybridization can never be wholly neglected. In certain cases this feature of change in the character becomes of great importance, overshadowing the mechanism by which the fundament of the character is transmitted. I am, of course, speaking here of permanent modifications in a character, and not merely of the temporary effects which may be produced in a heterozygous organism through the presence of other factors.

When we study the nature of mutations which are fundamentally morphological it first becomes evident that each mutation is essentially a cell change, transmitted as such to every cell of the organism through mitosis. Before considering this aspect of mutation let us classify some of the known types of morphological mutations. For this purpose we will consider chiefly the genus Oenothera where these types of change have been most fully studied. It seems clear that all or nearly all the changes to which I refer have originally taken place in the nucleus of the cell.

Referring first to chromosome changes, in the genus Oenothera the original number of chromosomes is 14. This is true of *Oe. Lamarckiana* and many other species. Duplication of one of these chromosomes through an irregular meiotic division has led to 15 in *Oe. lata,* a characteristic mutation which has occurred both in *Oe. Lamarckiana* and in certain races of *Oe. biennis.* The same chromosome number occurs in *semilata* and in a very different form from Sweden which I have called *incurvata.*[2] DeVries[3] has recently described still another form having 15 chromosomes. It was derived from *Oe. biennis semigigas* pollinated in part from *Oe. biennis*, and has flat leaves, whitish foliage, white veins, longer spikes, slender buds, small, erect flowers, thin cylindrical fruits and few seeds. Hence we may say that whenever a germ cell having 8 chromosomes fertilizes a normal germ cell a new form is produced, though what its characters will be depends upon various circumstances which need not be considered here. One of the most important of these factors is probably the particular combination of chromosomes received. It is perhaps not inappropriate to speak of all these mutants as belonging to the *lata* series, or the series with an extra chromosome.

Oe. mut. *gigas* is the prototype of another series of still more

[2] Op. cit., p. 147.

[3] DeVries, Hugo. 1915. The coefficient of mutation in *Oenothera biennis* L. Bot. Gaz. **59**: 169–196.

closely parallel mutations in which the chromosome series is doubled—28—the plant being a cell giant and not merely gigantic in its external dimensions. This mutation has not only occurred independently in two different strains of *Oe. Lamarckiana*, but a somewhat different giant having the same chromosome number occurred in Heribert-Nilsson's cultures of the Swedish *Lamarckiana*. Recently Bartlett[4] has found a tetraploid giant in his experiments with *Oe. stenomeres* which is an exact parallel to the previous cases in every particular.

A third series of morphological mutants is the *semigigas* series, having 21 chromosomes. This type of mutation has now been found in several species, including *Oe. Lamarckiana*, *Oe. biennis*, and hybrids of *Oe. Lamarckiana* or its derivatives with such species as *Oe. cruciata*, *Oe. muricata* and *Oe. Millersi*. Triploidy is thus much more frequent in its occurrence than tetraploidy, though the latter condition was discovered first.

Derivative from the above three types of chromosome change are various others. Thus a mutant from Sweden which I have called *latescens*[5] probably has 16 chromosomes, and by crossing and otherwise several additional numbers have been obtained.

The truth is obvious, not only that parallel mutations occur independently in different species, but that the type of change which gives rise to the extra-chromosome series is entirely different from that which produces the tetraploid series. I wish to point out that the nature of these changes is probably limited, and in this sense determined, by the structure of the germ plasm. In one group of organisms the mutations are of one kind, in another group they are wholly different in nature. This must be because the germ plasm in each group has its own particular lines of cleavage. Tetraploidy is a phenomenon which has occurred in a great variety of organisms, because the nuclear structure of almost any organism allows of its occurrence. Chromosome duplication, as in the *lata* series, is apparently much less common, but it may be expected to occur wherever the pairing of chromosomes in meiosis is weak and therefore liable to irregularities. Mutations then, in a sense, indicate where lines of weakness exist in the germ plasm, and it is these lines of weakness which define the particular directions which the mutations will take

[4] Bartlett, H. H. 1915. The mutations of *Oenothera stenomeres*. Amer. Journ. Bot. 2: 100–109, figs. 4.

[5] Op. cit., p. 117.

in any genus. Some of these "cleavage lines" are structural, some chemical in nature.

Another important feature of mutations which has not hitherto been emphasized is the fact that each is the result of a cell change which is represented in every part of the organism. This change originally occurred in the nucleus of a single cell, and the mitotic mechanism is responsible for handing it down to every part of the organism. The cells of *Oe. lata* constantly have 15 chromosomes, in whatever part of the plant they have been examined. Similarly in *Oe. gigas* even the most specialized tissues retain the double number of chromosomes transmitted to them,[6] though in the tapetal cells of all the forms secondary changes may take place, through fusion of nuclei and similar causes.

The conclusion follows that, with non-significant exceptions, every cell receives the number of chromosomes transmitted to it from the original fertilized egg. The blunt-pointed, deeply crinkled leaves, short stature, irregular branching, nearly sterile pollen, rounded buds and other features of *Oe. lata* are then an external expression of the fact that an extra chromosome is present in every cell. The real mutation was a cell change and is transmitted by mitosis as a cell change. Although we have at present practically no knowledge of the relation between cell structure and external form in organisms, yet we can at least affirm that the original change from a 14- to a particular 15-chromosome complex has resulted in the various external differences which we observe between *lata* and *Lamarckiana*. The organism is different because its every cell is different, and if in any part the extra chromosome should be dropped out into the cytoplasm through a slip in mitosis we should expect in that part a reversion to the foliage and other characters of *Lamarckiana*.

Viewed in this way, it is clear that we must consider the peculiarities of *lata* a result and not merely an accompaniment of the presence of the extra chromosome. We must, moreover, visualize the change as a cell change and the special features of *lata* as its external expression.

The same point of view applies probably to all other mutants. This makes comprehensible the fact that in many cases the mutants differ from the parent as strikingly in the early seedling stages as in the mature plant. The ontogeny of the new form does not witness a

[6] These and similar facts point to the conclusion that the chromosome divisions during ontogeny are not differential in nature, as Weismann supposed, but equational.

gradual drawing apart from its parent, except in so far as different organs may be unfolded in the later development. Already in the fertilized egg the difference is present, and makes itself felt as much in the first leaves as in the last. It is therefore important to remember that a mutant is such because not only its germ cells but every one of its somatic cells contains a certain peculiarity.

This is probably as true of animals as it is of plants, though an important difference is introduced here by the fact that in animals the germ cells are very early set apart from the somatic cells, while in higher plants this only happens with actual flower production.

If we compare the dimorphic condition of the cells in the males and females of certain insects with the difference between the cells of *Oe. lata* and *Lamarckiana*, it is clear that these differences correspond in certain features. The females of *Anasa tristis* have two members of a certain pair of chromosomes where the males have only one. Though the germ cells are set apart very early in the ontogeny in insects, yet it is probable that these chromosome differences occur not only in the young embryos, where they have been actually observed, but throughout the somatic tissues. A female animal, like a mutant, is somatically distinguished by having a different chromosome content in all its tissues, and not merely by the possession of female sex glands or secondary sexual characters. So far as I am aware, the fundamental significance of these facts in their bearing on heredity, embryology and variation, to say nothing of the structure of the cell, has not hitherto received attention, except in the case of cell giants. The fact that mutants differ from the parent in their every cell carries with it many important implications.

Giant mutations are now known in various organisms in the absence of tetraploidy. In such cases, although the cells are gigantic the chromosome number is unchanged. There is at present no clear indication of the fundamental nature of this type of cell gigantism. One of the best known instances is that of the giant variety White Queen Star, of *Primula sinensis*, described by Keeble.[7] This appeared in the normal variety and breeds true, but crossing experiments indicate that it may result from the presence of three independent factors. Various tetraploid giants of Primula have also been obtained.

No doubt there are many other types of chromosome change

[7] Keeble, F. 1912. Gigantism in *Primula sinensis*. Journ. Genetics **2**: 163–188, pl. 11.

besides those I have mentioned. These for the most part await discovery or investigation, although the cytological literature abounds with cases which are probably of this nature. One such instance, recently described, may be referred to here. In one of the grasshoppers, *Tettigidea parvipennis*, Robertson[8] found that certain individuals possess an abnormally long chromosome mated with a short one, while in other individuals the corresponding pair are of equal length. The explanation appears to be that a portion from the end of one chromosome became attached endwise to its mate. A study of the variability of these grasshoppers should be made, to discover whether any corresponding somatic change can be detected in those that have the long chromosome. It is suggested that negative mutations might be due to the loss of a portion from the end of a chromosome in this way.

In the remarkable phenomena of mutation in Drosophila studied by Morgan and his pupils, the new forms appear to result from changes in the nature of certain portions of particular chromosomes. The new characters are grouped in four series according to their hereditary behavior, corresponding to the four pairs of chromosomes, and in giving rise to each mutation a particular part of one chromosome may be assumed to have undergone a change.[9] This change is probably chemical in nature, at least in the series giving rise to the color varieties. The "crossing-over" phenomena, which have been studied in such detail by Morgan and his collaborators, are accounted for on the theory of the chiasma type of chromosome reduction, in which the chromosome pairs become looped around each other and so exchange segments of their substance. This process has not, I believe, been observed actually to take place in Drosophila.

In preparations of Drosophila chromosomes exhibited by Mr. Bridges, the somatic chromosomes appear to be remarkably closely paired and twisted about each other during the prophases of mitosis.

[8] Robertson, W. R. B. 1915. Chromosome studies III. Inequalities and deficiencies in homologous chromosomes: their bearing upon synapsis and the loss of unit characters. Journ. Morph. **26**: 109–141, pls. 3.

[9] The recent observations of Chambers (Some physical properties of the cell nucleus, Science, n. ser., **40**: 824–827. 1914) on the living spermatocytes of a grasshopper lend direct support to the view that the chromosomes are composed of discrete and more or less independent particles. He found that stimulation of the cell induces chromosome formation in the resting nucleus, and that the chromosomes are formed by the aggregation of definite granules in bunches about a hyaline core.

The suggestion therefore occurs to one that it may be in the premeiotic rather than the meiotic divisions of the germ cells that the "crossing-over" of material from one chromosome to its mate occurs. Personally I have never seen such an intimate relation between the members of chromosome pairs as is to be observed in the somatic cells of Drosophila. The absence of crossing-over in the male is, however, a difficulty with any hypothesis yet proposed.

Returning now to the subject of Oenothera, there is at least one mutation which is fundamentally chemical in nature. In the origin of *Oe. rubricalyx* we see exhibited the type of change which must occur whenever a new monohybrid Mendelian character appears. In all such cases it is only necessary to assume that one chromosome, or a portion of one, underwent a change in its chemical nature. The meiotic mechanism performs the function of distributing this chromosome and its descendants so that a Mendelian 3 : 1 ratio in the offspring will result.[10]

There have been many suggestions as to why the new character is dominant in one case and recessive in another. Cases like that of *Oe. rubricalyx*, in which the new character is dominant, are rare. It is possible that dominance may occur whenever the change results in the increased production of a substance, and recessiveness whenever there is loss of or reduction in the capacity for producing such a substance in the cell. This would apply to both dominant and recessive whites. Thus in the case of dominant White Leghorn fowls a substance is present in quantity which inhibits color production, while in recessive white flowers it is clear that the capacity for producing color has in one way or another, been almost completely lost or suppressed.[11] One may suppose that this color-inhibiting substance is one of the substances produced by the cells in all Leghorn fowls, but that in the White Leghorn it has been very largely increased through a chemical modification on the part of a chromosome.

In the present state of our knowledge it is impossible to determine the precise chemical nature of the change which produced *Oe. rubricalyx* from *Oe. rubrinervis*. The difference consists in an enormously increased capacity for anthocyanin formation in every cell of the

[10] For an explanation of later 15:1 ratios, see Gates, 1915, On successive duplicate mutations. Biol. Bull. **29**: 204–220.

[11] Of course this suppression may occur in various ways. Thus it has been suggested (Robertson, J. B. 1914. Bloodstock Breeders' Rev. Nos. 1, pp. 16–31; 2, pp. 91–107; Reviewed in Exp. Sta. Record **32**: 361. 1915) that in the gray horse,

organism, but especially in the buds. When the chemistry of the nucleo-proteins is better known, it may be possible to determine what chemical change one of them would have to undergo in order to increase the amount of anthocyanin produced by interaction with the cytoplasm of the cell, but these matters are as yet too complex for analysis, though much is being learned concerning the chemistry of anthocyanin and the physiology of its production in the cell.

Like the morphological mutations to which reference has already been made, there can be little doubt that *Oe. rubricalyx* is also a cell mutation, the nuclei in all parts of the organism containing a descendent of the original changed chromosome. Parallels to this mutation are found in such plants as the copper beech and the red sunflower, which belong to widely separated groups.

In conclusion, our complete lack of knowledge of the relation between internal cell structure and external form in organisms may be pointed out. Except in the relatively simple case of gigantism through tetraploidy it is quite unknown how a change in the nucleus of the cell-unit results in the external modification of characters. Why are the buds of *Oe. rubricalyx* more conspicuously red than any other part, and why are the leaves of *Oe. lata* blunt, the buds rounded, the pollen sterile, etc.? Before an answer to such questions can be attempted, something must be learned of the way in which the metabolism of the cell—a complex series of chemical activities—expresses itself in the form of structure involving relationship between differentiated cells and tissues.

which is a recessive, the grayness results from a structural modification in the canals which connect the pigment-producing cells with the hair follicles, rendering them too narrow for the passage of the pigment granules.